DETAILED ACTION

Claim 44 has been added. Claims 1-22, 27, 29, 34 and 36-39 have been canceled. Claims 23-26, 28, 30-33, 35 and 40-44 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The amendment filed 12-12-07 was not entered. The amendment filed 1-7-08 has been entered.

Applicant's arguments filed 12-12-07 have been fully considered but they are not persuasive.

Contrary to applicants statement on pg 4 of the response filed 12-12-07, the declarations filed in this application remain part of the prosecution history. The declarations were considered but were not found to be persuasive.

Claim Rejections - 35 USC § 112

Written Description

The rejection of claims 23-26, 28, 30-33, 35 and 37-43 under 35 U.S.C. 112, first paragraph, regarding the combination of "one or more" sugars, PEI and PEI derivatives in claim 23, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention has been withdrawn in view of the amendment.

New Matter

Support for applying a gene delivery complex comprising DNA and sugars, PEI or PEI derivatives “without the use of a needle” in claim 23 is found in the last line of the abstract (“a method for genetic immunization without a needle”). The specification teaches: "The complex can be infused using a pediatric feeding tube orally, vaginally or rectally in the case of human or animal adults or neonates… …Alternatively, the gene delivery complex may be packaged in a suppository and inserted in the vagina or rectum" (pg 17, lines 1-5).

While the specification contemplates transcutaneous application (pg 23, Table 2) and that the “complex can be applied on the skin or mucosa surfaces directly” (pg 16, line 34), direct application to the skin could be in the form of a subcutaneous injection (using a needle). Transcutaneous administration described in the specification was known in the art at the time of filing and encompassed injecting the skin (US Patents 5,257,980; 5390671; 5586553). Therefore, transcutaneous application (pg 23) and applying a complex “on the skin or mucosa surfaces directly” (pg 16) do not support "without the use of a needle” as claimed.

I. Claims 23-26, 28, 30-33, 35 and 40-44 are newly rejected as amended under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A gene delivery complex comprising “DNA and a sugar, or polyethylenimine, or polyethylenimine derivatives” in claim 23 is new matter. The phrase does not have

support in original claims 8-10, which are limited to a “gene delivery complex selected from the group consisting of DNA conjugates of sugars, polyethylenimine, polyethylenimine derivatives”. The scope now claimed is broader than the DNA conjugates of sugars, DNA conjugates of PEI and DNA conjugates of PEI derivatives contemplated in claims 8-10.

Enablement

The rejection of claims 37-39 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention has been withdrawn because the claims have been canceled.

Indefiniteness

The rejection of claims 23-26, 28, 30-33, 35 and 40-43 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of the phrase "whereby antigen presenting cells of said skin or mucosa are transfected" in claim 23 as amended.

The rejection of claims 23-26, 28, 30-33, 35 and 40-43 under 35 U.S.C. 112, second paragraph, regarding what applicants consider “applying” to the skin in claim 23 has been withdrawn in view of the amendment.

The rejection of claims 23-26, 28, 30-33, 35 and 40-43 under 35 U.S.C. 112, second paragraph, regarding a "gene delivery complex that targets antigen presenting cells" in claim 23 has been withdrawn in view of the amendment.

The rejection of claim 31 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of the amendment.

The rejection of claims 38 and 39 under 35 U.S.C. 112, second paragraph, has been withdrawn because the claims have been canceled.

II. Claim 30 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the phrase "method of claim 28, wherein the complex comprises a 5:1 ratio of mannosylated polyethylenimine nitrogen per DNA phosphate" remains unclear. It is unclear what applicants consider a mannosylated polyethylenimine nitrogen and how such nitrogens are distinguished from polyethylenimine nitrogen. Claim 30 does not clearly first limit the complex to having mannosylated polyethylenimine; therefore, limiting the complex to having a 5:1 ratio of mannosylated PEI nitrogen per DNA phosphate without first limiting the complex to one having mannosylated PEI does not make sense because the complex can made with sugar (see claim 23). Furthermore, the limitation in claim 30 does not further limit the "mannosylated polyethylenimine" of claim 26. Overall, the phrase is unclear.

Claim Rejections - 35 USC § 102

The rejection of claims 23-26, 28, 30-32, 35, 40, 41 and 43 under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e)

date=2-28-97) as supported by Carson (US Patent 5,679,647), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) has been withdrawn in view of the phrase "without the use of a needle" in claim 23 as amended and in view of Carson who was limited to intradermal injection of a gene delivery complex.

III. Claims 23-26, 28, 30-32, 35, 40, 41 and 43 remain rejected and claim 44 is rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) for reasons of record.

Parent application 60/058,933 did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Therefore, claim 23 does not get priority back to parent application 60/058,933 (filed 9-15-97). Parent application 09/153,198 (filed 9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9. Therefore, claim 23 has priority to 9-15-98.

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Behr taught administering any complex of the invention to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). More specifically, Behr taught topical, cutaneous, oral, rectal, vaginal, parenteral and

intranasal application (col. 6, lines 1-4), which is equivalent to applying the gene delivery complex to the skin or mucosa without the use of a needle as claimed.

The steps described by Behr encompass applying DNA encoding HIV by a number of means that do not require a needle; there is no reason to doubt the complex described by Behr would inherently transfect APCs because the steps are identical to those described by applicants. For example, applying a gene delivery complex topically as described by Behr inherently results in transfecting APCs as supported by Liu (see entire article).

Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Mittal taught luciferase induces antibodies in rats (second to last sentence of the abstract). Luciferase must be immunogenic as claimed in any animal other than fireflies because it is a protein isolated from fireflies and because proteins isolated from one animal and introduced into another animal are recognized as foreign by the immune system and cause an immune response (Kuby, pg 8-9). In the alternative, Behr taught the DNA could encode an HIV peptide (col. 3, lines 57-67).

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19).

The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Claim Rejections - 35 USC § 103

The rejection of claims 23-26, 28, 30-32, 35, 37-41 and 43 under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Carson (US Patent 5,679,647), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) and in view of Holler (US Patent 5,908,923) has been withdrawn in view of the phrase "without the use of a needle" in claim 23 as amended and in view of Carson who was limited to intradermal injection of a gene delivery complex.

IV. Claims 23-26, 28, 30-32, 35, 40, 41, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) and in view of Holler (US Patent 5,908,923).

Parent application 60/058,933 (9-15-97) did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Parent application 09/153,198 (9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9; therefore, claim 23 has priority to 09/153,198 (9-15-98).

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr taught the DNA could encode a peptide from HIV (col. 3, lines 57-67). Applying a gene delivery complex topically as described by Behr inherently results in transfecting APCs as supported by Liu (see entire article). The steps described by Behr encompass applying DNA encoding HIV by a number of means that do not require a needle; there is no reason to doubt the complex described by Behr would inherently transfect APCs because the steps are identical to those described by applicants. Case law established that reliance upon inherency in an obviousness rejection (103) instead of an anticipation rejection (102) is proper. In re Skoner, et al. 186 USPQ 80 (CCPA).

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Behr did not teach using a plasmid encoding a protein from a replication-defective, integrase-defective HIV.

However, Holler taught a plasmid encoding a replication-defective HIV that was integrase defective for use in vivo (col. 4, lines 51-54).

Thus, it would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a gene delivery complex comprising a plasmid encoding an HIV protein to the skin/mucosa of an animal as described by Behr, wherein the plasmid encoded a replication-defective, integrase-defective HIV as taught by Holler. One of ordinary skill in the art would have been motivated to make the HIV replication-defective and integrase-defective to prevent causing disease in the animal.

The combined teachings of Behr and Holler provide a reasonable expectation of successfully transfecting cells because Holler transfected CEM (a lymphoblastoid cell line) with integrase-defective HIV. Therefore, one of ordinary skill in the art at the time

the invention was made would have had a reasonable expectation of successfully transfecting APCs by applying the plasmid encoding the HIV taught by Holler to the skin or mucosa as taught by Behr.

Response to arguments

Applicants point out the advantage of the invention (pg 6). Applicants appear to be arguing unexpected results were obtained. Applicants' argument is not persuasive. Applicants do not teach the results obtained were "unexpected" as compared to the teachings of Behr combined with Holler or that "unexpected results" were commensurate in scope with the claims as broadly written (for any gene delivery complex administered by any means without a needle). Applicants have not established what were "expected" results from the teachings of Behr, added the "expected" results of Holler and then compared them to applicants' equivalent results. Comparing applicants' results to those of Behr alone is misplaced. Most importantly, the "advantages of the invention" fail to indicate applicants' results were "unexpected" over the teachings of Behr and Holler.

Applicants argue Behr is limited to gene therapy and not immunotherapy. Applicants' arguments are not persuasive. First, applicants' characterization of gene therapy is inaccurate. Gene therapy includes using DNA for any therapy. For example, Behr taught the DNA could encode an HIV peptide (col. 3, lines 57-67), which is an "immunogenic protein" as claimed. Alternatively, Behr taught using DNA encoding luciferase which inherently induces an immune response and meets the limitation of an

"immunogenic protein" in claim 23. The method steps claimed are taught by Behr, and they inherently result in transfecting APCs as supported by Liu.

Applicants' arguments regarding the "two classes of endeavors" on pg 7 of the arguments are noted but are not persuasive. Behr need not explicitly teach PEI would have allowed transfection of APCs when applied to the skin intradermally because it was known in the art (see Liu). Applicants' discussion of Behr throughout the paragraph on pg 7 fails to point out one distinction between the steps of Behr and the steps claimed.

Applicants' arguments regarding Carson are moot in view of the amendment and the new rejections.

Applicants argue Holler did not use the replication-defective retroviral vector in vivo. Applicants argue "method limitations are missing from both the other references." Applicants' argument is not persuasive. Holler has been relied upon for making the retrovirus replication defective and integrase defective and that the virus can be used in vivo. Applicants do not point to one specific step that the combined teachings of Behr and Holler fail to teach. Behr is relied upon for teaching the step of applying the DNA complex to the skin or mucosa without a needle. Holler need not teach all the method steps claimed.

Applicants' "Analysis" section on pg 9 of the response has been considered but does not point to one specific step that the combined teachings of Behr and Holler fail to teach.

Applicants imply the purpose of Behr is to induce a toxic immune response and point to col. 1, line 51. Applicants' argument is not persuasive. Behr is not limited to inducing a toxic immune response. Col. 1, lines 47-52, is part of the introduction and merely states: "Moreover, while recombinant viruses enable the efficiency of transfer of nucleic acids to be improved, their use presents some risks, such as pathogenicity, transmission, replication, recombination, transformation, immunogenicity, and the like." The sentence cited by applicants has nothing to do with applying a DNA complex to induce a toxic immune response.

Applicants cite references that taught low transfection efficiencies. Applicants' argument is not persuasive. Any efficiency of transfection is adequate to meet the limitations claimed.

Double Patenting

V. Claims 23-26, 28, 30-33, 35 and 40-43 remain and claim 44 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 08/803484 in view of the disclosure of '484. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 58 is drawn to a method for raising a cellular immune response in a mammal, the steps comprising transducing antigen presenting cells selected from the group consisting of Langerhans cells and dendritic cells with a plasmid DNA construct that encodes a replication-defective retrovirus, and exposing a mammal to the cells in a manner that allows the cells to express the construct in the lymphoid organs of the mammal, whereby a cellular immune response to the retrovirus

is raised by the mammal. Claim 58 could simply be drawn to a method of transfecting antigen presenting cells as now claimed in the instant application. The limitation of applying the gene delivery complex to the skin in claim 23 of the instant application encompasses intradermal administration, which is taught on pg 32, Example 14, (a). The genus of animal now claimed is obvious in view of pg 4, line 19, of '484. The limitation of one or more sugar, PEI or PEI derivative in claim 23 encompasses PEI delivery as on pg 38, line 20. The integrase-defective replication-defective retroviral vector in claims 38 and 39 of this application is obvious in view of claim 64 and Example 2 on pg 18 of '484. Two-way obviousness exists in this case because the teachings of '484 are incorporated by reference on pg 4, lines 29-32, of the instant application. The claims now in '484 can be claimed in the instant application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants do not argue this rejection or indicate willingness to file a terminal disclaimer. Rejections cannot be held in abeyance. Failure to argue the rejection or indicate willingness to file a terminal disclaimer is considered non-responsive. However, applicants' failure to argue the rejection or indicate willingness to file a terminal disclaimer has been overlooked in order to expedite prosecution. Applicants' next response must include arguments to the double patenting rejection or indicate willingness to file a terminal disclaimer.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

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